CHAVI RFA Question and Answer Document

QUESTION 1: On page 14 it says that "potential CHAVI investigators and their institutions other than the CHAVI Director and the Initial members of the scientific leadership group are not to be named in the application." On the other hand, a key component of the CHAVI is to write, in 50 pages, the research plan and the scientific plan upon which the grant will be judged. If the research plan is contingent on having vectors X, Y and Z available for development to solve the vector problem, can these sources be named and it documented that the vectors mentioned will be available? Otherwise if one writes, "we will develop vector X in the CHAVI", but show no source or no documentation of having it, then the review group will recognize this is a problem. This general concept applies to getting letters from computational biologists, structural biologists, etc. and others who will need to collaborate, join, be involved, etc. to give credibility to the research and strategic plans. Also, regarding the size of the scientific leadership group, the RFA mentions "to include the names of three to four initial members of the Scientific Leadership Group who will contribute to the planning, etc." Is the 3 to 4 membership of the SLG hard and fast? Can one go to 6?

ANSWER: We want you to demonstrate your understanding of the obstacles to HIV/AIDS vaccine development and vision for how to overcome them (in your SCIENTIFIC PLAN) and your capability to implement that vision in a new, innovative vaccine immunology center (in your STRATEGIC PLAN); these (and the Management & Operations Plan) are the crucial elements of the Application. Your concerns regarding the limitations on listing all of your potential collaborators in your application is based on a misunderstanding of the RFA. Perhaps we have not been clear enough so let us try to explain further. With the CHAVI RFA we are looking for an applicant with the capability and vision to establish and run an extramural HIV Vaccine Immunology Center comparable to the Vaccine Research Center on the NIH campus led by Dr. Gary Nabel. This is more than an effort to get a single vaccine into a clinical trial (as DAIDS funds through its IPCAVD and HVDDT awards). It is also more than a "gigantic IPCAVD" designed to get several vaccines into clinical trials. We want the Center to break new ground by doing targeted basic research in vaccine discovery and design, rather than just drive some already existing vaccine candidates through product development into clinical trials. But we also want the Center to understand and have the ability to do product development because pure basic research in the absence of a product development/manufacturing orientation can lead down impractical avenues.

We want the research to start with addressing the scientific gaps as identified by the Global HIV Vaccine Enterprise as stated in the RFA under Objectives and Scope ["(a) the elucidation of early immunologic and virologic events after HIV-1 exposure/infection in humans, including studies of exposed, uninfected persons and of HIV-infected persons during the acute to early stage of disease and/or; (b) the elucidation of the correlates of immune protection in non-human primate models in which there was protection from acquisition of infection (e.g., post-inoculation antiretroviral treatment to prevent establishment of persistent, productive SIV infection in macaques, or immunization with live, attenuated SIV and pathogenic virus challenge)."]. One or both of these specific priority areas should form the basis for the Director's starting research plan. The Application description of that plan should include the names of the scientists working on this in your lab and your key collaborators on that project, and document their availability as well as the availability of the necessary materials. But your "Scientific Agenda" should include much more than this focused research plan; it must present your understanding of the state-of-the-art, the key gaps in our knowledge, the obstacles to HIV/AIDS vaccine development, what you see as the opportunities for overcoming those obstacles, and a clear demonstration that you know how to turn this all into a product that can be tested in a clinical trial. We want you to assemble a small group of key collaborators (your Scientific Leadership Group) to develop this vision. But you don't need to document, by letter of support, that you have available all the specific vectors and specific technical expertise (e.g. computational biologists and other experts) that you will need to implement your vision because we expect your vision to evolve. Your CV

and your discussion of your HIV/AIDS vaccine accomplishments to date will list most of these experts anyway. Your CV plus, very importantly, your Strategic Plan will demonstrate to the Review Panel that you know how to find and sign on the appropriate scientific/product development/manufacturing partners. Actually, if you document the availability of all the products and partners you plan to include too specifically then you may be giving Review the impression that you just plan to drive some already existing vaccine candidates into clinical trials instead of breaking new ground in vaccine development. We want you demonstrate your knowledge of the different vectors, their advantages and disadvantages and how you will choose between them and/or improve on them, rather than argue how the one vector that you have nailed down access to is the best. We can fund the vaccine candidates already out there into clinical trials by already existing mechanisms; we want the CHAVI to develop new vaccine candidates, based on new basic research that will address the above stated Enterprise scientific priorities and the need for induction of persistent mucosal/systemic immune responses. We will explain this to the Review Panel so they will not be looking for the sort of availability documentation for research and development activities to be initiated in years 2 to 7 that they would normally expect to see in an IPCAVD application or HVDDT proposal.

As for the budget, that should be, as stated in Section 6 of the RFA, divided into three major sections (Management and Operations; Research Program; Shared Scientific Resources/Facilities). The Research Program for which you write a budget is the Director's Research Plan. The research budget will expand in years 2 to 7 as more research activities are added but the Director's research plan in your application is what you are to describe in detail in the research budget (with a broad outline of the expansion plans). Similarly, you should be able to provide detail about the Management & Operations budget and the initial Shared Scientific Resources/Facilities budget (also with expansion plans in broad outline) in your application without listing a lot of potential collaborators. We will expand on how to write the budget sections in the answer to a separate question to be posted soon on this web site.

Let us add another important reason for limiting the early involvement of a large number of collaborators in the Scientific Leadership group named in the application. If the applications contain long lists of potential collaborators then it will quickly become impossible to put together a competent review panel because of conflicts. This is a very important initiative and we are sure you want the Review Panel to be of the highest quality.

QUESTION 2: Does the funding for the first year include indirect costs for the institution or will the indirects be added?

ANSWER: The $15 million figure is total costs; it includes indirect costs.

QUESTION 3: My research is focused on modified envelope constructs that should have the potential to induce broadly cross-reactive neutralizing antibodies. I notice that one of the Global HIV Vaccine Enterprise "Scientific Priorities" listed (3.1.iii) is to "Launch a large-scale, multi-approach attack on the neutralizing antibody (Nab) problem." However, in the CHAVI RFA you ask for the Director's Research Program to focus on one (or both) of two other of the Enterprise scientific priorities (3.1.i "vaccine design based on the characteristics of viruses causing early infection" or 3.1.ii "identify potential immune correlates of protection against SIV in selected monkey model systems"). Does this mean that the CHAVI is not supposed to tackle the neutralizing antibody problem? Another investigator I know believes that the immune response to HIV facilitates establishment of infection and thus the task should be to induce tolerance to viral antigens. Is her/his approach also outside the bounds of the CHAVI? Basically my question is whether NIAID has a list of acceptable and unacceptable vaccine development approaches for the CHAVI to pursue.

ANSWER: While the initial research of CHAVI should focus on one (or both) of the Enterprise priorities listed in the RFA, additional research activities should be described in the application's Scientific Agenda - based on the applicant's vision of the obstacles/opportunities in HIV/AIDS

vaccine development. New vaccine product development should then build on the scientific results generated by the research. NIAID has no list of acceptable/unacceptable HIV/AIDS vaccine approaches; indeed NIAID hopes that different approaches will be submitted to challenge our thinking about HIV/AIDS vaccine development. The two approaches listed in your question are both acceptable. The strength, merit and coherence of the applicant's Scientific Agenda and Strategic Plan for its implementation will be evaluated by a peer review panel tasked with assessing the application's (and applicant's) potential to develop critical new knowledge about HIV immunology that will advance HIV/AIDS vaccine development. However, that said, the caveat is that you must convince the review panel of the scientific value of your position.

QUESTION 4: In the use of animal models, are models of vaccine induction that results in non-sterilizing immunity appropriate? These would be models like the SHIV 89.6 model, looking at immune correlates, and the Harriet Robinson and John Shiver models of vaccine induced protection from disease progression.

ANSWER: No. In order to advance the development of a prophylactic HIV vaccine the Global HIV Vaccine Enterprise has identified as a scientific priority the identification of potential immune correlates of protection in those animal models where significant protection against the acquisition of established infection has been observed. Vaccines that allow establishment of infection with better control of viral load are important areas of research but are not the goal of this effort; these sorts of studies and vaccine constructs are being supported by other NIAID programs.

QUESTION 5: Are studies of humans infected with HIV (with antibodies and in some but not all cases CTL) who are able to maintain virtually undetectable viral loads (below 50 copies) in the absence of HAART part of the scope of work envisioned?

ANSWER: A qualified yes. If the plan is to search in early infection for a correlate of this "protection" that may extend into vaccine design or even just to describe how widespread this phenomenon may be in a developing country that could be the setting for an eventual efficacy trial then it is within in the scope of the CHAVI RFA as it is the investigation of early immunologic and virologic events after HIV-1 infection. However, if you plan to study a population here in the US and/or one that has been infected for a long time (long term non-progressors) this is not within the scope of the CHAVI RFA.

QUESTION 6: To what extent is the focus of this project expected to be international?

ANSWER: This is an international pandemic and while the PI must be based in a domestic institution, the scope of vaccine discovery and certainly the clinical trials must occur in populations most affected by the epidemic so that the final product of CHAVI is indeed a vaccine where it is most needed. Thus international collaborations are encouraged, especially if you plan to focus initial research on the Enterprise priority of "elucidation of early immunologic and virologic events after HIV-1 infection in humans, including studies of exposed, uninfected persons and of HIV-infected persons during the acute to early stage of disease, with a focus on collaborating with HIV vaccine trial sites in resource-poor settings."

QUESTION 7: To what extent will the track record of the PI in leading collaborative efforts related to immunology or vaccines influence the decisions?

ANSWER: The CHAVI will have several different, although related, tasks: vaccine discovery (based on solid immunology and virology research), vaccine design, vaccine product development, and early phase clinical trials. Obviously a PI cannot be a leader in all these areas (the Scientific Leadership Group should complement the PIs expertise), but as we're really trying to address the immunological roadblocks to the discovery of a vaccine, expertise and leadership

in immunology is crucial. The quality of the PI with respect to research accomplishments (track record), vision and leadership capability (in leading collaborative efforts) will be a critical factor evaluated by Peer Review. In some senses you could view this RFA as being as much about identifying a strong CHAVI director as about the specific proposed research.

QUESTION 8: Is the project intended specifically for someone who has been active in testing vaccines in the past, or is it appropriate for someone like me who has been doing HIV immunology?

ANSWER: We are looking for dynamic leadership, total commitment to the mission and a passion to make and deliver an HIV vaccine. Even if you have only been focused on basic HIV immunology up to now, with little or no involvement in vaccine development, you could still be a good candidate for CHAVI director. But be prepared to learn a lot of new stuff about vaccine product development, GMP manufacturing and regulatory compliance, and you would be well-advised to include someone with vaccine development experience in your Scientific Leadership Group.